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**The information in this document is no longer current. It is intended for reference only.**

## EXECUTIVE SUMMARY

The Division of Epidemiology, Statistics, and Prevention Research (DESPR) conducts a research program in the field of reproduction and maternal and child health, as part of the Intramural Research component of the National Institute of Child Health and Human Development (NICHD). Historically, epidemiology and biometry appeared on the organizational chart of the NICHD in 1967, as the Epidemiology and Biometry Branch. The Branch became the Epidemiology and Biometry Research Program in 1970. The Program was renamed as the Division of Prevention Research in 1990, and became the Division of Epidemiology, Statistics, and Prevention Research in 1991. Dr. Mark Klebanoff was appointed Acting Director in 1998, and Director in 1999.

The Division consists of the following components:

- The Office of the Director (OD) provides overall supervision and guidance of the research activities of the Division. The OD also is responsible for planning and conducting the proposed Longitudinal Cohort Study of Environmental Effects on Child Health and Development. In addition, the OD contains the Collaborative Studies Unit, the extramural component of the Division, which is responsible for managing the District of Columbia (D.C.) Infant Mortality Initiative. The OD maintains a small program of epidemiologic research, usually in collaboration with the other Branches of the Division.
- The Epidemiology Branch conducts most of its research in human fecundity and fertility, pregnancy complications, preterm birth and fetal and infant growth, child health status and injuries, and pediatric infectious diseases and vaccine evaluation. The Branch also contains the Pediatric Epidemiology Section, which focuses on birth defects.
- The Prevention Research Branch provides a focus within the NICHD for behavioral research in health promotion and disease prevention. Its major interests lie in the prevention of problem behaviors among adolescents and behavioral interventions to prevent childhood injuries.
- The Biometry and Mathematical Statistics Branch (BMSB) conducts research in statistical methodology and provides statistical consultation to the research staff of the Division and other components of the Institute. Methodological research projects of the Branch often derive from problems identified during consultations.
- The Computer Sciences Section (CSS) provides first-line support to the Division regarding computer software, systems, and data management. The Section also provides data management support to several investigators in another component of the NICHD Intramural Program, the Division of Intramural Research (DIR).

In addition to the Division Director, new individuals were appointed as Chiefs of all three Branches: Dr. Bruce Simons-Morton was appointed Chief of the Prevention Research Branch in July 1997; Dr. Germaine Buck was appointed Chief of the Epidemiology Branch in September 2000; Dr. Kai Fun Yu was appointed Chief of the BSMB in September 2000.

The Division has undergone extensive changes in response to the report of the 1996 Board of Scientific Counselors' site visit. In particular, it has sharpened its research focus to concentrate on the areas of reproductive and perinatal epidemiology, prevention of problem behaviors and injuries in children and adolescents, and the epidemiologic investigation of childhood injuries. Division researchers have established a productive collaboration with the Laboratory of Developmental and Molecular Immunity (LDMI) in the DIR, and this collaboration will continue. The Division has implemented formal procedures for developing research ideas from Division staff, and has developed procedures to increase communication and collaboration, both between and within the Branches of the Division. Virtually all of the Division's research is conducted through the research contract mechanism, which means DESPR is heavily dependent on a stable and predictable NICHD contracting budget. Small pilot studies and laboratory support projects are funded through the Division's direct operating budget.

In addition to its research, the Division encourages its members to participate in professional societies and to serve the Institute, the National Institutes of Health (NIH), and the U.S. Government in a variety of ways. Since the last report to the National Advisory Child Health and Human Development (NACHHD) Council in 1997, Division members have:

- Served as President of the Society for Pediatric and Perinatal Epidemiologic Research (1998-9, 2001-2), and as Vice President and Program Chair of the Society for Public Health Education (1998-9);
- Regularly reviewed manuscripts for a variety of professional journals;
- Reviewed abstracts and coordinated abstract reviews for professional societies, including the Society for Epidemiologic Research, Society for Pediatric and Perinatal Epidemiologic Research, Society for Public Health Education, American Public Health Association, and the Society for Pediatric Research;
- Served or are serving on the Editorial Board of the *American Journal of Epidemiology*, and as Associate Editors of the *American Journal of Epidemiology*, *Health Education Research*, and *Reproductive Toxicology*;
- Served on the NICHD Institutional Review Board;
- Acted as a Planning Committee Member for the U.S. Surgeon General's Report on Youth Violence;
- Served as members of the Transportation and Mobility Advisory Group for the National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention (CDC); and
- Served as the NICHD liaison to the American Academy of Pediatrics Committee on Injury and Poison Prevention, and on advisory boards of the National Research Council and the Institute of Medicine of the National Academies of Sciences, the American Chemistry Council, the Gynecologic Oncology Group, the Maternal and Child Health Bureau, and the March of Dimes.

In addition, several Division members hold adjunct faculty appointments and/or have served on dissertation committees at Johns Hopkins University, the University of Maryland, George Washington University, Mount Sinai School of Medicine, the University of Buffalo, and the

University of Albany. DESPR staff have also given named lectures at the University of Rochester and at Boston University.

DESPR is deeply involved in the mainstream of epidemiologic, prevention, and public health research. The remainder of this report summarizes the research accomplishments of the Division.

### **OFFICE OF THE DIRECTOR (OD)**

In addition to providing overall direction and guidance to the Division, the OD maintains a small research program. The research of the OD is focused largely on various risk factors for adverse pregnancy outcomes. The OD is also responsible for planning and conducting the proposed Longitudinal Cohort Study of Environmental Effects on Child Health and Development. The OD Collaborative Studies Unit manages the D.C. Infant Mortality Initiative.

### **ABNORMAL GENITAL FLORA AND PRETERM DELIVERY**

The association between maternal genital tract infection and adverse outcomes of pregnancy is among the most active areas of investigation in both obstetrics and perinatal epidemiology. As part of his role as a member of the steering committee of the NICHD Maternal-Fetal Medicine Units Network, Dr. Mark Klebanoff, Director of DESPR, served as co-chair of the protocol subcommittee that directed the recently completed, randomized clinical trials of treatment of bacterial vaginosis and trichomoniasis during pregnancy to prevent preterm birth. In these two clinical trials, 1,953 women with bacterial vaginosis and 617 women with trichomoniasis were randomized to receive 2 g of either metronidazole or placebo. Although this treatment regimen effectively eradicated the infections, it did not significantly reduce preterm birth among women with bacterial vaginosis who were treated with metronidazole compared to a placebo. Results of the bacterial vaginosis trial played a key role in the recent recommendation of the U.S. Preventive Services Task Force against routine screening and treatment of bacterial vaginosis in the general obstetrical population.

In addition to these disappointing trial results, bacterial vaginosis continues to be associated with a variety of adverse health outcomes including preterm birth, spontaneous abortion, pelvic inflammatory disease, post-genital tract surgery infection, and HIV acquisition. However, little is known about how bacterial vaginosis is acquired and maintained, or why this condition is more than twice as prevalent among African American women compared to other women. To determine the factors associated with the incidence of abnormal vaginal flora, researchers from the OD, in collaboration with researchers from all three Branches of DESPR are collaborating with researchers from the University of Alabama at Birmingham in the Longitudinal Study of Vaginal Flora. In this study, researchers are following several thousand women, utilizing vaginal Gram stains every three months, for one year. At entry and quarterly time periods, biologic specimens are collected, and the women complete a detailed questionnaire on hygienic,

sexual, dietary, and other practices. The study will evaluate associations between changes in these practices and the incidence of bacterial vaginosis.

### **CAFFEINE INTAKE, SPONTANEOUS ABORTION, AND REDUCED FETAL GROWTH**

The relationship between maternal caffeine intake during pregnancy and several unfavorable outcomes, particularly spontaneous abortion and reduced fetal growth, is controversial. There have been many positive and negative studies of these outcomes, with no obvious correlation between the quality of the study and the nature of the results. To evaluate the nature of the relationship, researchers from the OD and the Epidemiology Branch conducted a study of the association between maternal serum paraxanthine (caffeine's primary metabolite) concentration and the occurrence of spontaneous abortion and fetal growth restriction.

Serum paraxanthine was found to be unassociated with the occurrence of spontaneous abortion, except at very high concentrations corresponding to caffeine intakes of approximately six cups of coffee per day. Paraxanthine was not associated with reduced fetal growth among women who did not smoke. However, among smokers, higher serum concentrations of paraxanthine were associated with an increased risk of fetal growth restriction. These findings are predominantly reassuring and suggest that for most women, particularly those who do not smoke, moderate caffeine consumption during pregnancy is unlikely to carry a great risk.

### **PREGNANCY AND CHILDHOOD EFFECTS OF *IN UTERO* EXPOSURE TO ORGANOCHLORINE COMPOUNDS**

Dichlorodiphenyldichloroethylene (DDE), a major, persistent metabolite of the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT), which was widely used in the past, has both estrogenic and anti-androgenic properties. This raises the possibility that DDE may contribute to genital tract malformations such as hypospadias and cryptorchidism, as well as to a possible decline in sperm counts over the past 50 years. Although several incidents of heavy exposure to polychlorinated biphenyls (PCBs), a family of organochlorine compounds with many industrial uses, resulted in reduced birth weight and adverse childhood neurodevelopment, the effects of more usual levels of these compounds are uncertain.

Investigators in the OD, in collaboration with investigators from the Epidemiology Branch of the National Institute of Environmental Health Sciences (NIEHS), have utilized serum samples from the Collaborative Perinatal Project to address these questions. The Collaborative Perinatal Project is a prospective cohort study of pregnancy and childhood, conducted by the NIH from 1959, to 1974. This serum bank is uniquely suited for such a project, as relatively high levels of exposure to these organochlorine compounds were more common in the 1960s than more recently. Results to date indicate that high maternal serum concentration of DDE during pregnancy was associated with moderately elevated risks of hypospadias, cryptorchidism, and supernumerary nipples, all of which are markers of deficient androgen action *in utero*. High maternal serum concentration of DDE was also associated with a threefold increase in the risk of

preterm birth and a doubling of the risk of small-for-gestational-age (SGA) birth. Analysis of the association between maternal serum PCB concentration and child development is ongoing.

### **LONGITUDINAL COHORT STUDY OF ENVIRONMENTAL EFFECTS ON CHILD HEALTH AND DEVELOPMENT**

The Children's Health Act of 2000 authorized the NICHD to "investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes." This study will follow about 100,000 children across the U.S., identified as early *in utero* as possible, through birth, childhood, and into adulthood. The term "environment" is broadly defined to include chemical, physical, and social/behavioral influences on children. The planning process for the study emphasizes strong partnerships between federal and non-federal scientists and community, parent, advocacy, and industry groups. Planning and organization of the study are currently underway, with a number of activities in progress to consider aspects such as hypotheses and study design, ethical issues, use of emerging technologies to measure exposures and outcomes, and community outreach/participation. Some of these activities include public meetings, development of a strategic plan, and implementation of an advisory committee and a working group structure. Background information on the Longitudinal Cohort Study is available at [www.nichd.nih.gov/despr/cohort](http://www.nichd.nih.gov/despr/cohort).

### **THE COLLABORATIVE STUDIES UNIT**

#### **NICHD-D.C. Infant Mortality Initiative**

The OD, through its Collaborative Studies Unit, continues to collaborate with the NIH Center for Research on Minority Health to sponsor the D.C. Initiative to Reduce Infant Mortality. The Initiative is currently preparing to start a clinical trial to learn more about the psychosocial and behavioral risk factors that can influence the occurrence of adverse pregnancy outcomes. The clinical trial will take place in five prenatal clinics located in the D.C. area.

Another project within the Initiative is evaluating the effectiveness of interventions aimed at delaying sexual activity among young teens who live D.C. If the pilot proves successful, this program will be expanded into a full intervention study to take place in 22 schools.

A third project within the Initiative, funded by the National Institute on Alcohol Abuse and Alcoholism, will expand on a pilot study to screen pregnant women in prenatal care settings for any alcohol use.

## EPIDEMIOLOGY BRANCH

The Epidemiology Branch actively conducts research within the domain of reproductive, perinatal, and pediatric epidemiology. Research initiatives focus primarily on human reproduction, pregnancy, infant and child health, and injuries. Depending upon the intended study outcome, research may be conducted in the U.S. or abroad. Current areas of research interest and expertise include: determinants of human fecundity and fertility; gravid health status including hypertensive disorders of pregnancy; preterm delivery; fetal growth; birth defects; infectious diseases in pregnant women and children; child growth and health status; and injury prevention. Despite a relatively small cadre of epidemiologists in the Branch, a plethora of research papers stem from its research activities; many have important implications for a diverse body of scientists, clinicians, and public health officials. Branch investigators serve on a number of prestigious national and international boards, panels, and advisory committees, in addition to providing leadership and service to professional organizations and other governmental agencies. The Branch continues to recruit, train, and retain talented investigators to complement and expand its research mission within the NICHD.

What follows is a brief description of some of the Branch's leading research initiatives since the last DESPR Report to the NACHHD Council in 1997. The description is organized into five sections:

- Human fecundity and fertility
- Pregnancy
- Birth defects
- Pediatric infectious diseases and vaccinology
- Child health including injuries

The sections are presented in a manner intended to reflect the continuum of reproductive, perinatal, and pediatric endpoints starting with preconception endpoints, and ending with child health and injury prevention, all of which comprise the research portfolio of the DESPR Epidemiology Branch.

### **HUMAN FECUNDITY AND FERTILITY**

Research in this area focuses on factors that affect male and female fecundity, defined as the biologic capacity for reproduction and fertility or birth outcomes. Such research may study men and women separately, or as a couple when outcomes are couple-dependent such as conception.

#### **PCBs, Pesticides, and Female Fecundity and Fertility**

There is growing public and scientific concern about the relation between chemicals and human reproduction and development. Findings from experimental animal and wildlife studies have reported adverse effects on reproductive and developmental endpoints following exposure to PCBs and select pesticides. Given the ubiquitous nature of many of these contaminants in the environment, interest into their potential effects on human health status continues to increase.



Branch investigators recently began to analyze data collected in earlier research initiatives that were funded by another government agency, the Agency for Toxic Substances and Disease Registry (ATSDR) to determine if serum concentrations of PCBs and pesticides affect time-to-pregnancy, risk of early or late pregnancy loss, and infant health status including birth size (H75/ATH298328). Approximately 100 women who were planning pregnancies were recruited and interviewed prior to becoming pregnant. Women were prospectively followed for 12 at-risk menstrual cycles, or until they became pregnant; blood specimens were collected over time. Analysis of these data is currently underway. This study will provide important and timely data on a spectrum of endpoints relative to serum concentrations of PCBs and pesticides.

### **PCBs and Risk of Endometriosis and Polycystic Ovarian Syndrome (POS)**

Another related environmental contaminant/reproductive health study is a case control study of PCBs and risk of endometriosis and POS. Endometriosis and POS are gynecologic disorders that affect a substantial proportion of women of reproductive age; both disorders are associated with fecundity- and fertility-related impairments. Although the etiology of these disorders remains elusive, recent animal data suggest that endocrine disrupting chemicals may be involved in their pathophysiology. To address this question in humans, a case control study was undertaken to determine whether serum concentrations of PCBs increase risk for endometriosis or POS. Branch investigators are currently analyzing data collected as a part of a study that was previously funded by the NIEHS (R011ES09045).

### **Declining Sperm Counts: an Autopsy Study**

The quality of human semen has reportedly been declining since the beginning of World War II, with sperm counts declining possibly by as much as 50 percent. Currently, Branch investigators are addressing this concern by studying testicular parenchyma from 600 men who underwent autopsy examination between 1930-1959, and 1996-1999. All of the men died suddenly and had no underlying infectious or chronic diseases. The numbers of round spermatids, primary spermatocytes, and Sertoli cells per gram of testis parenchyma will be used to compute daily sperm production, and determine changes in sperm count over time. The study is sufficiently powered to identify a significant 10 percent reduction in counts between the two time periods.

### **PREGNANCY**

Branch investigators conduct various studies that focus on pregnancy-related health outcomes. Many of these studies address hypertensive disorders such as preeclampsia. Other pregnancy-related outcomes studied by Branch investigators include randomized clinical trials to determine the efficacy of interventions for preventing preeclampsia or for treating spontaneous abortion. Timely new research initiatives regarding the study of promising biomarkers of exposure, disease, and susceptibility are underway as well, stemming largely from the biologic specimen banks established as a part of clinical trials.

## **Trial of Calcium for Preeclampsia Prevention (CPEP)**

Successful completion of the CPEP Study, a double-blind, randomized, clinical intervention trial described in the previous Council Report, revealed that daily supplementation with 2,000 mg of calcium did not reduce the incidence or severity of preeclampsia, nor did the supplement delay its onset. The wealth of accurately recorded information in the CPEP database, in addition to the valuable CPEP specimen repository are being utilized for a variety of follow-up studies. Some examples are given below.

### **Prostacyclin and Thromboxane Changes Predating Clinical Onset of Preeclampsia**

Excretion of the urinary metabolites prostacyclin and thromboxane was measured from timed urine collections that were obtained prospectively from women enrolled in the CPEP Trial. Women who developed preeclampsia had significantly lower levels of prostacyclin metabolites throughout their pregnancies, even at 13-to-16 weeks' gestation. Gestational age-adjusted levels were 17 percent lower than those of normotensive women. Levels of thromboxane metabolites were not significantly higher overall. However, the ratio of thromboxane metabolites to prostacyclin metabolites, used to express relative vasoconstricting versus vasodilating effects, was 24 percent higher in preeclamptic women throughout pregnancy when compared to normotensive women. The results suggest that reduced prostacyclin production, but not increased thromboxane production, occurs many months before the clinical onset of preeclampsia and may explain why aspirin fails to prevent the condition.

### **Maternal Calcium Supplementation and Fetal Bone Mineralization**

To determine the effect of maternal calcium supplements during pregnancy on fetal bone mineralization, researchers followed infants of 128 women randomized to calcium in the CPEP Trial and 128 women randomized to the placebo group, who were enrolled at one clinical center. Dual-energy, x-ray absorptiometry measurements were performed during the infants' first week of life. Total body bone mineral content was significantly greater in infants born to calcium-supplemented mothers than in infants born to mothers who had received a placebo, among women who receive less than 600 mg per day of dietary calcium. The conclusion was that maternal calcium supplementation of up to 2 g per day during the second and third trimesters can increase fetal bone mineralization in women with low dietary calcium intake. Calcium supplementation in pregnant women who have an adequate dietary calcium intake, however, is unlikely to result in major improvement in fetal bone mineralization.

### **No Evidence for Lipid Peroxidation in Severe Preeclampsia**

Recently, it has been hypothesized that increased generation of reactive oxygen species may contribute to the genesis of preeclampsia. However, the interpretation of these changes in conventional markers of oxidative stress has been constrained by such issues as nonspecificity of the route of formation of the analyte, imprecision of the analytical method, and *ex vivo* lipid peroxidation. To address this issue more definitively, the generation of the major urinary isoprostane, 8,12-*iso*-iPF<sub>2α</sub>-VI, was assessed using mass spectrometry in a prospective study of healthy nulliparas from the CPEP Study who developed severe preeclampsia. Isoprostanes are free radical catalyzed prostaglandin

isomers formed from arachidonic acid. When measured with specific assays, analysis of these compounds in urine provides a specific, sensitive, and noninvasive approach to the quantitation of lipid peroxidation *in vivo*. Of the study population of women matched on clinical centers, date of enrollment in the CPEP Trial, and gestational age, 29 developed severe preeclampsia, compared to 29 unaffected women. No significant differences were observed between the two groups of women with respect to urinary 8,12-*iso*-iPF<sub>2α</sub>-VI before or at diagnosis, nor was there any variation by gestational age. These findings suggest that lipid peroxidation and, hence, oxidative stress is not increased in severe preeclampsia.

### **Ethnicity, Nutrition, and Birth Outcomes in Healthy Nulliparous Women**

This study assessed ethnic differences in birth outcomes to examine whether the outcomes were related to differences in nutrition. Nutrient intakes were estimated from a 24-hour recall at 13-21 weeks' gestation and included total caloric intake, protein, carbohydrate, fat, and 13 vitamin and mineral constituents. African-American women were significantly more likely than non-Hispanic white women to have a preterm or small-for-gestational-age (SGA) infant, even after adjusting for medical center and maternal height, weight, and smoking, or when further adjusting for all nutritional variables. Calcium supplementation did not have a significant effect on the risks of poor birth outcomes, even among those with a very low dietary calcium intake (<400 mg/day). Differences in birth outcome between white non-Hispanic and Hispanic women were small and were not significantly influenced by nutritional variables. Within the Hispanic group, Spanish speakers had substantially better nutrition and modestly, but not significantly, better birth outcomes than English speakers. After adjustment for all nutritional and non-nutritional covariates, no significant increases in risk of SGA or preterm birth were observed for Hispanic English-speakers as compared to Hispanic Spanish-speakers. It appears that in the U.S. nutritional differences may not account for unexplained ethnic differences in birth outcome.

### **EFFECTS OF EPIDURAL ANALGESIA ON LABOR AND DELIVERY**

Epidural analgesia is a safe and effective method for pain relief during labor and is used on more than 50 percent of pregnant women in the U.S. Despite its increasing popularity, questions have been raised about its relation with prolonged labor and increased use of instrumental (e.g., forceps) or operative delivery. In collaboration with the U.S. Army, a study was designed to address the effects of epidural analgesia on clinical aspects of labor and delivery, at a large tertiary hospital that serves military personnel and their families. Use of epidural analgesia increased from 1 percent of deliveries before October 1993, to 70 percent the following year, thereby, allowing for a unique research opportunity. Nulliparous women with singleton vertex pregnancies and who entered labor spontaneously between 37 and 42 weeks' gestation were studied. Use of an epidural during labor did not increase the risk of cesarean delivery, fetal head malpositioning, oxytocin use, or instrumental delivery for dystocia. The length of active phase of labor appeared unchanged, but the second stage of labor was prolonged by 25 minutes. A significant, 21-fold increase in risk of hyperthermia was associated with epidural analgesia. The

exact meaning of this relation is unknown, but raises important considerations for the clinical management of women during labor. Further research in this area is planned.

### **A MULTICENTER RANDOMIZED TRIAL ON MANAGEMENT OF EARLY PREGNANCY FAILURE**

Pregnancy failure during the first trimester occurs in approximately 15 percent of clinically recognized pregnancies. For more than half a century, dilatation and curettage (D&C) has been a standard of care for early pregnancy failure. D&C remains one of the most common operations, accounting for two-thirds of outpatient gynecologic surgeries. Although D&C is safe, it increases risk of cervical laceration, uterine perforation, endometrial adhesions, pelvic inflammatory disease, and secondary infertility. Recently, D&C has been challenged as the standard of care for uncomplicated early intrauterine pregnancy failure, and several observational studies have reported effectiveness rates ranging from 56 percent to 70 percent for pharmacologic treatments, such as with misoprostol or gemeprost. To address the efficacy, safety, and acceptability of medical management versus surgical management for pregnancy failure, Branch investigators are implementing a large, randomized clinical trial. Approximately 800 women whose pregnancies end in an incomplete miscarriage or fetal death before 13 weeks' gestation will be recruited during a 24-month period from four clinical centers in the U.S. Women will be randomized to either the D&C or misoprostol treatment group. At each clinical visit, women will be interviewed and examined for side effects, complications, and any anxiety associated with treatment, as well as for overall acceptability of the treatment. This study is currently underway.

### **BIRTH DEFECTS**

#### **Minimum Dose of Folic Acid to Prevent Neural Tube Defects (NTDs)**

Preconception folic acid supplementation reduces the risk of NTDs. Although the U.S. Public Health Service recommends that women of childbearing age who are capable of becoming pregnant take a 400-microgram folic acid supplement, the minimum effective dose is not known. An effective dose is one that raises the amount of a woman's red cell folate to a level known to be associated with low-risk for NTDs. Many women do not follow the recommendation, which prompted the U.S. Food and Drug Administration to mandate fortification of enriched grain products with folic acid. To determine how much folic acid is really needed to be effective, Branch investigators conducted a double-blind trial that randomized women to one-of-four groups: placebo group, 100 microgram folic acid supplement group, 200 micrograms folic acid supplement group, or 400 micrograms of folic acid daily. Red cell folate levels significantly increased in all three treatment groups. The observed increases were estimated to result in approximately a 22 percent, 41 percent, and 47 percent reduction in NTD risk for women in the three treatment groups, respectively. The actual reduction could be greater because compliance was not optimal; furthermore, long-term exposure could increase the benefits of being in positive folate balance. This study demonstrates that the current food fortification program in the U.S. is likely to reduce the incidence of NTDs substantially.

#### **Effects of Thermolabile Methylenetetrahydrofolate Reductase**

Homocysteine has become the focus of many studies because it is a marker for cardiovascular disease and has a purported relation to NTDs. One major pathway for the elimination of homocysteine is methylation of the compound to form methionine. This requires the production of methyl folate from methylene folate, via the enzyme methylenetetrahydrofolate reductase or MTHFR. There is a variant of the gene for MTHFR (C677T) that produces an abnormal variant of the enzyme, the thermolabile form. Branch investigators examined the effect of the MTHFR homozygous thermolabile variant (MTHFR-TT) on folate status and found that women with MTHFR-TT genotypes had significantly lower red cell folate levels than women with wild type MTHFR. This finding suggests that people with MTHFR-TT may have lower cellular folate levels than those without it. Such individuals may be at increased risk of having fetuses and infants with NTDs. As a result, this population may require higher intakes of folic acid than currently recommended for U.S. populations.

### **Cleft Lip and Cleft Palate**

As mentioned, there is a consensus that folic acid can prevent many NTDs. Whether or not folic acid can prevent oral clefts is much more controversial. Clinical trials of vitamins in the prevention of oral clefts and observational studies of vitamins and clefts have produced inconsistent results. Clefts are believed to have a genetic component, but folate-related genes have received little attention. Branch investigators conducted a case-control study to determine whether MTHFR-TT is a risk factor for isolated cleft palate, or for cleft lip with or without cleft palate. Genotyping was performed on members of the Cleft Lip and Palate Association of Ireland and on a control group randomly selected from the virtually universal Irish neonatal screening program. Cleft lip with or without cleft palate was somewhat, but not statistically significantly associated with MTHFR-TT. MTHFR-TT conferred a significant threefold increased risk for isolated cleft palate, which suggests that MTHFR-TT may be involved in the etiology of this defect. Furthermore, this finding might explain the inconsistent effects observed for folic acid in previous studies, in that only women with this gene would be at-risk of having an affected offspring. Work is continuing in this area.

### **PEDIATRIC INFECTIOUS DISEASES AND VACCINOLOGY**

This avenue of study addresses both infections during the perinatal period and in childhood, as well as the clinical indications of promising new vaccines. Infections continue to be a leading cause of death, especially for young infants and children throughout the world. Much of the Epidemiology Branch's research in this area is conducted with collaborators from the U.S. Navy, the CDC, and investigators from the Laboratory of Developmental and Molecular Immunity (LDMI) of the NICHD. Branch investigators continue their efforts aimed at the early identification and treatment of perinatal and pediatric infections to minimize sequelae, including death, using experimental designs of the highest scientific integrity.

## **The Effectiveness of Risk-Based Intrapartum Chemoprophylaxis for the Prevention of Early Onset Neonatal Group B Streptococcal (GBS) Disease**

GBS is an infectious disease that can cause considerable illness in newborns, pregnant women, and susceptible nonpregnant adults. The use of intrapartum antibiotic prophylaxis (IAP) as an intervention strategy that targets parturient women with risk factors for GBS was recommended by the CDC in 1996. These recommendations were based solely on a decision analysis, rather than on a randomized trial of the risk-based approach. Given that randomized controlled trials are considered unethical for assessing the effectiveness of IAP (i.e., a placebo control group), Branch investigators addressed this question using a case-control design. Cases (infants with early onset GBS) and controls (infants without GBS) were selected from infants born to mothers with risk factors for delivering newborns with GBS disease. Mothers of cases and controls were compared for their receipt of intrapartum antibiotics to assess its effect on the reduction of risk of early onset GBS disease in their offspring. Overall, the effectiveness of IAP was 86 percent, which increased to 89 percent when the first dose of intrapartum antibiotics was given two or more hours before delivery. These data provide the scientific underpinning for the risk-based approach to IAP for prevention of an early onset GBS disease.

## **Assessing IAP and Increased Late-onset GBS Disease in Infants**

IAP is effective in preventing early onset GBS disease in infants. Since the publication of the national guidelines for prevention of perinatal GBS disease in 1996, the incidence of early onset disease has been declining over time. Surveillance data show an unanticipated increase in late-onset disease in the presence of declining early onset disease. As IAP is directed only against early onset GBS disease, and given the reappearance of maternal GBS carriage after antibiotic treatments, questions were raised as to whether the maternal IAP defers the occurrence of GBS disease to later dates, rather than preventing transmission of GBS to the infants. Branch investigators launched a case-control study to assess the relation between maternal IAP treatment and delivery of an infant with late-onset GBS disease. Cases (infants with late-onset disease) and controls (infants without GBS disease) born to mothers with published risk factors for GBS are being studied to determine the effect of IAP on subsequent development of GBS in infants. Analysis is currently underway and is intended to help interpret the enigma of declining rates of early onset GBS amidst rising rates of late-onset GBS.

## **Maternal Capsular Polysaccharide GBS and the Delivery of Neonates with Early Onset GBS**

It has been shown that titers of serum Immunoglobulin G (IgG) anti-serotype specific GBS antibodies in mothers protect newborns from early onset GBS disease. Because an understanding of the relationship between these titers and GBS is crucial for evaluating new vaccines against GBS, Branch investigators have launched a prospective, multicenter, case-control study involving six collaborating centers in the U.S. Researchers are comparing cases (infants with early onset GBS) and controls (infants who are free of disease despite being colonized by GBS). Maternal and cord sera taken at the time of delivery are subsequently assayed for serotype-specific IgG antibodies using enzyme-linked immunosorbent assay (ELISA) techniques. These comparisons and assays for titers of homologous maternal and cord antibodies will enable investigators to learn more about the relationship between antibody titers

and risk of early onset disease, as well as any protective thresholds. Data collection is complete and analyses are currently underway.

### **Evaluations of a New Oral Enterotoxigenic *Escherichia coli* (ETEC) Vaccine**

ETEC is the most common cause of pediatric diarrhea throughout the world. It causes more than 650 million episodes of diarrhea in children less than five years of age, annually. Recently, a killed, oral ETEC vaccine composed of recombinant cholera toxin B subunit (rBS), which is antigenically similar to the heat-labile toxin of ETEC, together with formalin-killed ETEC cells expressing colonization factor antigens I, II, and IV, was developed by Svennerholm and colleagues in Sweden. In collaboration with the U.S. Naval Medical Research Unit in Cairo, Egypt, Branch investigators have undertaken a program of research to evaluate the vaccine in Egyptian children. Specifically, the study will assess whether the vaccine reduces the burden of disease due to ETEC and evaluate its effect on the nutritional status of the population. Phase II trials of the killed, oral ETEC vaccine were already conducted in Egyptian adults, children, and infants. Results show that the vaccine has no major side effects and is immunogenic in this population. A Phase III trial to measure the clinical efficacy of the vaccine is presently underway in the Abu Homos district of the Beheira Governorate. About 240 children between six- and 18-months of age have been vaccinated with either the ETEC vaccine, or a K12 placebo. Follow-up of children for ETEC diarrhea is underway.

### ***Helicobacter pylori* Infections in Children**

*Helicobacter pylori* infections are known to cause gastric mucosal atrophy and hypochlorhydria. Because the gastric acid barrier is an important host resistance factor against many enteric infections, Branch investigators are conducting studies to evaluate the relationship between *H. pylori* infection and the risk of subsequent diarrheal illnesses in children. A study is currently in progress in rural Egypt that has enrolled more than 250 infants who are under active surveillance for diarrheal illnesses and *H. pylori* infections. Investigators are performing periodic anthropometric measurements on these children to assess whether *H. pylori* infections affect growth and result in impaired nutritional status. Researchers are also collecting breast milk and blood specimens to evaluate whether levels of antibodies modify the risk of acquisition of infection. The findings of this study will provide useful information for vaccine development and design of interventions against *H. pylori*.

### **Field Trials of a New Vi Polysaccharide Conjugate Vaccine for Typhoid Fever in Children**

Typhoid fever, caused by *Salmonella typhi*, remains a common, but serious infection for many children throughout the developing world. Typhoid fever is a disease that has become difficult to treat, so promising vaccines offer hope for many. Vi polysaccharide vaccine is licensed in approximately 70 countries, and, along with two other licensed typhoid vaccines, is known to offer a 70 percent immunity among individuals five years of age or older. To address this, scientists in the LDMI of the NICHD linked Vi to a recombinant exoprotein A of *Pseudomonas aeruginosa* (Vi-rEPA) and developed a conjugate vaccine. In collaboration with investigators from the DESPR Epidemiology Branch, Phase I and II studies were conducted to evaluate the safety and immunogenicity of the Vi-rEPA vaccine. These studies found that the conjugate was immunogenic in children aged five-to-14 years, and induced a booster response in children two-to-five years of age. A randomized, double-blinded trial of approximately 12,000 Vietnamese

children aged two-to-five years was conducted to evaluate the safety, immunogenicity, and efficacy of the Vi-rEPA vaccine for typhoid fever. The vaccine had an efficacy of 92 percent, the highest ever reported for a typhoid vaccine. Vi-rEPA was shown to be safe and immunogenic in children two-to-five years of age. The high level of both IgG and Vi antibodies and efficacy of the vaccine indicate that Vi-rEPA will be at least as protective in individuals less than five years of age. Plans are underway to evaluate the immunogenicity of Vi-rEPA when administered with the Diphtheria/Tetanus/Pertussis vaccine in infants.

## **CHILD HEALTH**

The Branch conducts research focusing on the health and well-being of infants and children, including the relation between intrauterine events and adult health, or the so-called “fetal origins of a disease” hypothesis.

### **Influence of Perinatal Factors on Subsequent Growth and Development**

There is increasing appreciation that intrauterine environment may affect long-term health status, which supports the hypothesis that adult disease may have fetal origins. In collaboration with colleagues at the National Center for Health Statistics, Branch investigators used data from the Third National Health and Nutrition Examination Survey (NHANES III) to study children who were low birth-weight (LBW), preterm, and/or classified as SGA (< 10<sup>th</sup> percentile of birth-weight-for-gestational-age) to assess their health status through age six years. Approximately 7,800 birth certificates were obtained and linked to children aged two months through six years, who were included in the NHANES III sample. At any given weight, body fat appeared relatively higher for SGA children, supporting a link between disturbances in intrauterine growth and obesity-related chronic disease. Breastfeeding did not significantly reduce child overweight, nor was any reduction in fatness observed for increasing duration of breastfeeding. Children who were LBW or preterm at birth were found to have small, but measurable delays in motor and social development throughout early childhood, in comparison to children of larger size or born at-term. These data support earlier findings and underscore the need for targeted intervention for children born early and at smaller birth sizes to maximize their development and well-being.

### **Maternal Determinants of Childhood Immunizations and Other Health Outcomes**

In the U.S., early childhood immunization rates are currently near or at record high levels, albeit low rates still exist in many urban areas. A recent report by the Institute of Medicine emphasized the need to eliminate socioeconomic disparities in vaccine compliance in the U.S. Because a proper understanding of determinants for under immunization is a necessary precursor for the development of effective interventions to improve full immunization, Branch investigators, in collaboration with several Washington, D.C. universities and hospitals, undertook a prospective birth cohort study to determine factors that predict failure to immunize children in a timely fashion. Researchers interviewed 369 mothers shortly after delivery and between three-to-seven and seven-to-12 months postpartum. Approximately 75 percent of infants three months of age were fully vaccinated; this figure dropped to 41 percent at seven months of age. Only 53 percent of infants who were fully vaccinated at three months of age



were so at seven months of age. Factors associated with being fully vaccinated at seven months of age included lower birth order and maternal employment. Most parental psychosocial factors, such as self-efficacy and perceived social norms, were not associated with immunization status. This study underscores public health challenges in achieving complete and uniform immunization for all infants and children, and the need to design targeted and acceptable interventions for at risk sub-populations of mothers and children.

## **CHILDHOOD INJURIES**

An additional avenue of Branch research focuses on injuries. Branch investigators are working to describe the scope and magnitude of fatal and non-fatal injuries occurring in infants, children, and adolescents, and to formally evaluate the efficacy of intervention strategies targeted at specific causes of death, such as drowning.

### **Fatal Injuries in Infants**

Injuries are the leading cause of death among children and the third most common cause of death in the second-through-12 month of life. Branch investigators analyzed linked birth and death records for U.S. infants to assess risk factors for death from injuries. Cause of injury-related deaths were (in descending order): homicide, accidental suffocation, motor vehicle crashes, choking, fire, and drowning. Factors such as maternal age, education, and use of prenatal care were more strongly associated with injury death than infant characteristics, such as gender and birth weight. However, infants with lower birth weights were at significantly greater risk of death due to inhalation of food or objects, than infants of larger birth size. Risk factor profiles for deaths classified as undetermined intent (4 percent) were compared to profiles for other injury deaths and were found to resemble more closely deaths from intentional, rather than unintentional, injuries. This suggests that fatality rates from intentional injuries are underestimated. Deaths of undetermined intent and homicides comprised 23 percent of injury-related deaths. Factors most strongly associated with these types of deaths included maternal age less than 17 years, late or no prenatal care, and having a second or third child by age 19. These findings underscore the need to identify at-risk mothers to allow interventions that reduce injury-related deaths among their infants.

### **Childhood Drowning**

Drowning is a leading cause of injury-related death in the U.S., with particularly high rates for toddlers of all ethnic groups and African American males 10-to-19 years of age. During the past four years, Branch investigators have continued investigations into the epidemiology of childhood drowning, in part, with colleagues from the Consumer Product Safety Commission. Specifically, researchers obtained and analyzed death certificates for 1,420 childhood drowning deaths (persons <20 years) in 1995. The site of drowning was specified on 1,311 (92 percent) death certificates. In children one-to-four years of age, 56 percent of drowning deaths occurred in artificial pools, while 27 percent were in other bodies of fresh water such as lakes and rivers. Among older children (age five-to-15), site-specific drowning rates varied by ethnicity. Importantly, the risk of drowning in a swimming pool was more than 11 times greater among African American males aged 10-to-19 years compared to white males of the same age.

### **Pilot Study to Evaluate Swim Lessons and Risk of Drowning**

Branch investigators conducted a pilot study to determine the feasibility and costs of conducting a case-control study evaluating whether swim lessons reduce the risk of drowning among children. Through active surveillance in 22 counties in Washington State and California, researchers identified 23 eligible submersion victims, aged one-to-six years. For each drowning death, controls were sought using multiple selection strategies, the most successful of which were block-walk (identified controls for 86 percent of drowning cases) and random digit-dialing (identified controls for 72 percent of drowning cases). Multiple strategies for contacting and interviewing families of drowning victims also were piloted with encouraging results. Plans are underway for further study.

### **Nonfatal Injuries among Children in D.C.**

In 1998, nearly 140,000 deaths in the U.S. were attributed to injuries, accounting for over 50 percent of deaths among children. Fatal injuries comprise only a small fraction of the overall injury burden, yet there are no mechanisms for uniformly recording or reporting such injuries. In collaboration with investigators from several universities and hospitals in Washington, D.C., Branch investigators developed a city-wide surveillance system to identify all fatal and serious nonfatal injuries among resident children aged zero-to-two years. From October 1, 1995, through September 30, 1996, 3,039 injury-related hospital visits were identified, yielding an annual event-based rate of 13.5 visits per 100 persons. Annual injury rates were highest in children aged one-to-two years (19.3 injuries per 100 persons) and lowest in infants (8.2 injuries per 100 persons). After one year of age, rates were higher for males when compared to females. Annual injury rates varied by residence, ranging from 3.4 to 24.1 injuries per 100 children. Intentional injuries and injuries where intent was undetermined, but suspected of being intentional, comprised the largest fraction of deaths (44 percent) and hospitalizations (22 percent). In addition, researchers reviewed circumstances surrounding the injury event for all hospitalizations and for a sample of emergency room visits. Preliminary analyses suggest that approximately half of the injuries could have been prevented with passive strategies (e.g., removal of environmental hazards), and possibly 85 percent with active prevention strategies (e.g., better supervision of the child or improved safety practices in the home).

## **PREVENTION RESEARCH BRANCH**

Originally, the Prevention Research Branch was established as a Section in 1990; it received Branch designation in 1992. The mission of the Prevention Research Branch is to conduct research examining the prevalence and identify determinants of health behaviors and to test the effectiveness of educational, behavioral, and environmental strategies to improve or protect maternal, child, and adolescent health. Since the last DESPR report to the NACHHD Council in 1997, the Branch's research has focused on the health-related behavior of children, adolescents, and parents. Its largest program of research focuses on assessing and improving adolescent health behavior, including preventing problem behaviors and risky driving. Another program of research focuses on parent-child management of childhood disease and injury risk. Several studies are observational in design and seek to determine prevalence and identify determinants of health behavior. Other studies, such as *Going Places* (prevention of problem behavior among middle school students) and the Young Driver Intervention Study, test the efficacy of interventions in randomized trials. Descriptions of the major studies in the Branch are described in the following pages.

### **YOUNG DRIVERS INTERVENTION STUDY (CHECKPOINTS)**

Motor vehicle crashes are the leading cause of injury and death among adolescents (defined as ages 15-to-19). Most states have adopted graduated licensing policies that increase supervised-practice driving, delay licensure, and restrict initial licensing privileges. The effectiveness of these policies has been attributed to the specific provisions adopted, and to their effect on altering perceived norms and parental management of teen driving. Programmatic efforts to increase parental management of teen driving are underway, but little research has addressed this issue to date. The Young Drivers Intervention Study is designed to test the effect of persuasive communications on the adoption of the Checkpoints Parent-Teen Driving Agreement and on the increase of parental management of teen driving. The Checkpoints Program is designed to increase parental restrictions on teen driving and reduce risky driving, traffic violations, and crashes during the first two years of licensure. Families are recruited from the Connecticut Department of Motor Vehicles when a teen applies for a learner's permit; the teen is then randomized to the special intervention condition or usual information control condition. Preliminary research by the Branch shows that parental management reduces risky driving by teens. In addition, a pilot study demonstrated that exposure to several persuasive communications significantly increases adoption of the Checkpoints Parent-Teen Driving Agreement.

### **PREVENTING PROBLEM BEHAVIOR AMONG MIDDLE SCHOOL STUDENTS (*GOING PLACES*)**

Middle school is a challenging transition for many youth, and smoking, drinking, other drug use, and violent and delinquent behaviors increase dramatically during this period. The *Going Places* Study is designed to assess the prevalence of, identify predictors of, and prevent increases in problem behaviors among middle school students. Seven middle schools in one Maryland school district were assigned to either the special intervention, or usual education condition, in a

group-randomized trial. The special intervention includes a problem-solving curriculum, school-level changes, and parent education. In analyses published to date, the research team has documented a higher rate of smoking and drinking among whites than African Americans; identified unique peer and parent influences on smoking and drinking among boys and girls; identified adjustment problems associated with bullying and victimization; and identified predictors of violent behavior. The study provides a rich database for analyses of observational data. Preliminary analyses of treatment group differences provide evidence that exposure to the intervention increased parental involvement and prevented some problem behaviors.

### **VIOLENCE PREVENTION AMONG HIGH-RISK YOUTH**

Prevention of youth violence is a national priority. Branch researchers are involved in several violence-prevention studies with high-risk youth. Presently, the Branch is testing the application of ideas from the *Going Places* problem-solving curriculum to an individual approach with high-risk youth. The study tests the effects of an individualized intervention approach on school adjustment, academic engagement and motivation, and problem behavior. In one school, high-risk sixth graders who were identified through a baseline survey are recruited, asked to provide consent (parent and youth), and randomized to the special intervention, or the information-only control group. Those in the special intervention group are pulled from one class each week (a different course each week) for eight weeks to meet with a trained educator/mentor. Working from a semi-structured intervention protocol, the mentor trains the youth in problem-solving approaches that can be applied to interpersonal conflict, school achievement, and other problems that the youth identifies.

A second youth-violence prevention initiative is a collaboration with investigators from Children's National Medical Center. In this study, researchers are developing and pilot-testing an intervention protocol for youth between the ages of eight and 12, who present to the emergency room injured in a fight. The youth intervention is based, in part, on work developed for *Going Places*, but in this case, learning activities will be delivered by trained mentors who are drawn from an existing mentor-training program. The study objectives are to decrease pre-adolescents' exposure to dangerous situations and peers, and to increase their involvement in adult-supervised, pro-social activities. The youth intervention teaches problem-solving techniques that will enable teens to resolve interpersonal conflict and reduce their exposure to high-risk situations and people. Additionally, family interventions are designed to increase parental monitoring and expectations for pro-social activities and peer affiliation.

### **TAILORED PERSUASIVE COMMUNICATIONS FOR PEDIATRIC INJURY PREVENTION**

As mentioned, injuries are the leading cause of death and a major cause of morbidity in young children. The majority of these injuries occur in the home or car; many could be prevented or minimized through the use of appropriate safety measures. The use of individually tailored educational materials in primary care settings may be an effective and efficient way to promote adoption of injury-prevention measures by parents. This study is designed to test the effectiveness of individually tailored, injury-prevention information that is provided in a

pediatric clinic on the adoption of injury-prevention measures. Researchers recruited parents from a well-child clinic in Washington, D.C., and then assigned them to receive either generic, or tailored injury-prevention information. In findings submitted for publication, the research team has documented greater adoption of injury-prevention measures among parents who received tailored information, than among those who received generic information, with the largest effects occurring among those who received tailored information and discussed that information with their physician. A future study will examine the effect of combined, tailored, parent and physician information on the promotion of physician-parent communication in regard to injury prevention and the adoption of injury-prevention behaviors by parents.

### **BIOMETRY AND MATHEMATICAL STATISTICS BRANCH (BMSB)**

The BMSB is the statistical component of DESPR. Branch staff works closely with epidemiologists and prevention researchers in the role of statistical collaborators and act as the primary statisticians of the projects that the BMSB supports. The BMSB is responsible for the statistical and applied mathematics activities of DESPR. It conducts research in statistical theory and methodology relevant to research in the areas of maternal and child health, growth and development, and related fields. The Branch develops quantitative procedures appropriate for application in the biomedical and life sciences and consults and collaborates with intramural and extramural scientists on statistical and mathematical problems.

### **COLLABORATIVE AND CONSULTING ACTIVITIES**

The primary goal of the BMSB is to provide statistical expertise to NICHD research activities through consultation and collaboration. Senior staff members of the BMSB provide statistical consultation and engage in independent statistical research with investigators inside and outside the NIH. The following are research highlights from the past five years.

#### **Problem Behavior Prevention**

The goal of this study is to develop, implement, and test the efficacy of a multi-component program of school-based interventions in the primary prevention of problem behavior in a sample of middle school students. A BMSB staff member has been involved as the principal statistician of the project since its inception. This staff member has participated in the design of the project, the review of proposals from competing contractors, and the analysis of collected data.

### **The Longitudinal Study of Vaginal Flora**

This prospective, observational study aims to advance knowledge of the natural history and abnormal alteration in vaginal microbial flora. The study also hopes to identify risk factors associated with these alterations. A BMSB staff member has been involved as a statistician in the project from its beginning in 1998.

### **Declining Sperm Count: an Autopsy Study**

The purpose of this project is to determine the number of round spermatids, primary spermatocytes, and Sertoli cells per gram of testis parenchyma and to compute daily sperm production per gram of tissue. The study involves 300-400 coroners' cases from Olmsted County, Minnesota, that were autopsied in between 1930, and 1959, who died suddenly in the absence of chronic disabling disease.

### **SGA in Alabama and Scandinavia**

BMSB staff continues to analyze data collected in these projects. Recent research includes findings in otitis media in early childhood and developmental outcome at age five. This study examines the impact of otitis media on developmental outcomes using a Scandinavian sample from the SGA Study. A total of 714 children at five years of age participated in this study, in three Scandinavian sites, Bergen and Trondheim in Norway, and Uppsala in Sweden.

### **Human Growth Hormone (HGH) Trials**

The NICHD and Eli Lilly & Co., have two trials evaluating height of children treated with HGH. One trial is for short, normal children, while the other trial is for girls with Turner's Syndrome. The trials have a yearly meeting of the data safety and monitoring board, at which a Branch statistician reports all trial statistics.

### **Hermansky-Pudlak Syndrome (HPS)**

HPS is a genetic disease of the pulmonary system. The NICHD is conducting a randomized, double-blind, placebo-controlled trial of pirfenidone in the treatment of HPS. A BMSB statistician presents interim data analyses for this trial to the data safety and monitoring board, once a year.

### **GBS Diseases**

As explained earlier in this report, GBS is an important health risk for newborns. A Branch statistician has been involved in the analysis of a case-control study of GBS. This analysis led to the planning of a case-control study to determine whether IAP merely shifts the timing of early onset GBS to late-onset GBS.

### **Osteogenesis Imperfecta (OI)**

OI is a genetic disease of connective tissue, which leads to bone fracture and growth disorders. Improving bone density is an important goal for treatment of OI. The natural history of bone density for Type III and IV OI has been analyzed. It was found that bone density increases more rapidly in Type IV OI than in Type III. The relationship between bone density and spine

compression has also been studied. A trial was planned to study treatment of OI with pamidronate and growth hormone to increase bone density.

### **The Third National Health and Nutrition Examination Survey (NHANES III)**

NHANES III has been a source of many growth studies. A statistician from the BMSB has been involved in the analysis of three such studies. The first study sought to determine if exclusively breastfed infants differed in size from other infants, and if such differences persist through age five. The second study examined whether or not there were independent effects of birth weight and gestational age on motor and social development, through age four. The third study described ethnic differences in changes in weight, stature, and body mass index in children before age seven.

## **STATISTICAL RESEARCH ACTIVITIES**

Most methodological research problems the BMSB deals with are motivated by the consultative and collaborative projects mentioned in the previous section. As a result, the nature of the Branch's statistical research projects is quite variable. The following projects were selected to reflect the current research activities of the staff members.

### **Confidence Intervals for the Odds Ratio in Case-Control Studies**

In the analysis of case-control data, confidence intervals for the odds ratio by existing methods are too large. This is true of both conditional and unconditional methods. Shorter confidence intervals can be obtained by a simultaneous consideration of both tails of the distribution. A BMSB staff member developed a procedure that produces shorter intervals than existing procedures.

### **Multiple Comparison Procedures that Control the False Discovery Rate**

In some multiple testing applications, control of the chance that any false discovery will be made is too restrictive. An example is genetic micro-array data, in which thousands of genes provide separate sites for possible statistical testing; in such testing problems, one may wish to control the false discovery rate. Procedures have been developed that control the false discovery rate and are much more powerful than procedures that control the possibility of any false discovery. Researchers have also found procedures to control the false discovery rate either on-average, or absolutely.

### **Sample Size Calculation for Estimating the Reference Range**

With laboratory variables, it is often of interest to establish reference ranges, commonly taken as the 2.5 percent and 97.5 percent points of the variables' distribution. Currently, a deterministic criterion is used for sample size calculations, which is not appropriate except for cases involving Gaussian data. However, lab data are rarely Gaussian. A more reasonable, probabilistic criterion is offered for sample size requirements in such studies. A BSMB staff member has developed a general method, using a statistical technique called "the bootstrap" to calculate required sample sizes for the probabilistic criterion.

### **Conditional Estimation Following Group Sequential Trials**

Group sequential trials are designed so that accumulating data can be periodically examined, to allow a trial to be stopped early if sufficient evidence of treatment effect is observed.

Previously, estimation methods did not include the stepping time for such trials as a condition for estimation. Methods were developed that are less conditionally biased for this estimation and confidence interval problem.

### **Power of Wilcoxon's Test for Shift Alternatives**

In comparing two populations with distinctly non-Gaussian values, one often plans to use Wilcoxon's rank-sum test. An Edgeworth expansion method was formulated to estimate power from pilot data. Simulation was used to compare the most practical methods of power estimation. It was found that "the bootstrap" method is generally more reliable, but that the Edgeworth expansion method can give a lower bound on the power which could be useful.

### **Comparison of Two Sequences of Probabilities**

A simple comparison measure for two sequences of probabilities is the squared distance between these two sequences. This test is shown to be more powerful particularly for the case when one sequence is not majorized by the other.

### **Common Odds Ratio under Cluster Sampling**

The estimation of the common odds ratio of  $K$   $2 \times 2$  contingency tables using the beta-binomial sampling scheme, where the number of clusters and the cluster sizes are different is being investigated. The variance of the asymptotic distribution of the Mantel-Haenszel estimator is developed when the number of tables becomes larger while the numbers and sizes of clusters in each table are bounded.

### **Longitudinal Data Analysis**

The BSMB has investigated varying coefficient regressions models with repeated measurements. Specifically, a two-step smoothing method has been proposed to solve some estimation problems. Large-sample properties and confidence bands for component-wise varying coefficient regression with longitudinal dependent variable. The Branch has also explored a method for assessing parametric and semiparametric regression with longitudinal dependent variable. Some standard models for fetal ultrasound measurements, such as Rossavik models, logistic models, and linear models, have been studied using Successive SGA Study data. The findings indicate that Rossavik model fits the ultrasound data best.



## **COMPUTER SCIENCES SECTION (CSS)**

The CSS provides computing capability for the DESPR staff to keep members current with the latest technology and to help maximize productivity. Specifically, the technical support of CSS includes the following areas:

### **PROVIDING EPIDEMIOLOGIC AND STATISTICAL COMPUTING EXPERTISE**

The CSS provides computing expertise to the Division by advising on computing approach, doing ad hoc programming for individual projects, and creating general-purpose programs for use by all of DESPR. The CSS also supports individual staff members and their collaborators in programming and analyzing research data on many studies carried out in the Division.

### **PROVIDING CENTRAL PROCUREMENT AND MANAGEMENT OF HARDWARE AND SOFTWARE**

The CSS maintains a complete hardware inventory of all computing equipment in the Division and is responsible for allocating the equipment in the most effective way to maximize DESPR computing. Through close cooperation with the Information Resources Management Branch (IRMB) in the NICHD Office of Administrative Management (OAM), the CSS plans for new computer requirements and the redistribution of exiting computers in the Division, to maximize the use of current inventory equipment, and keep up with the diverse and growing computer needs of the Division.

The CSS also maintains a complete software inventory, procuring what is necessary to ensure that the Division staff has the software it needs and that it is using properly licensed, legally acquired software. The CSS, as the central coordination point for computing resources in the Division, also orders service for malfunctioning equipment and upgrades for software.

### **PROVIDING EXPERT DATA MANAGEMENT GUIDANCE**

The CSS provides a backup system for data stored on personal computers and on the UNIX workstations, to ensure that valuable data is not lost in cases of hardware malfunction or accidental destruction of files.

The CSS provides consultation on an ad hoc basis to scientists in the Division, and occasionally elsewhere in the NICHD, on the transfer of data between collaborators, both within the NIH and outside (foreign and domestic). CSS staff is expert in data formats and all types of storage media for mainframe and personal computers.

### **SERVING AS HELP-DESK TO DESPR STAFF**

Members of the Division can consult with the Section at any time, on any computing problems. DESPR staff are requested to come to the CSS to report malfunctioning hardware or software.

### **ACTING AS LIAISON BETWEEN DESPR STAFF AND SOURCES OF TECHNOLOGY**

As the central computing service in the Division, the CSS serves as liaison to other technical organizations, to represent the needs of the Division and to make the services available in outside organizations available to Division staff. The CSS maintains ongoing relationships with the Local Area Network (LAN) coordinators and the IRMB for smooth interface with the network. In that role, the CSS makes requests to the LAN administrators for services and software to be added to the LAN, coordinates the addition and release of network accounts for DESPR personnel, and disseminates information from the LAN administrators to DESPR internal users.

In addition, the CSS regularly interacts with such organizations as the Center for Information Technology (CIT) on technical issues; with the NICHD OAM and the IRMB on procurement issues; and with sales representatives who provide technical goods and services on current developments in the field.

### **MANAGING COMPUTING ACCOUNTS AND COMPUTING CONTRACTS**

Currently, the Section manages two contracts to supplement its internal programming and data-processing capabilities: 1) a task-order contract to provide data analysis and statistical programming to DESPR and to certain other groups within the NICHD; and 2) a contract for analysis of complex, multistage, sampling survey data. The CSS participates closely with the NICHD Contracts Management Branch in writing the statements of work and other portions of requests for proposal, evaluating responses, selecting contractors, defining new tasks, and evaluating contractors' work in progress. The Section assumes day-to-day responsibility for technical liaison and overall management of these projects.

In addition, the Section serves in a consulting capacity with regard to the computing components of other research contracts in the Division. The CSS is also responsible for administering the Division's computer accounts at CIT and on the Sun Workstations, obtaining accounts for new staff members or contractors and seeing to the orderly cleaning and releasing of unused accounts.

## APPENDIX 1: DESPR PERSONNEL

### OFFICE OF THE DIRECTOR (OD)

**Mark A. Klebanoff, M.D., M.P.H.**, is a pediatrician and epidemiologist who joined DESPR's Epidemiology Branch in 1983. He was appointed Acting Director of DESPR in 1998, and Director in 1999. His research interests span a broad range of topics in the epidemiology of maternal and child health, but focus on the preterm delivery and fetal growth.

**Cassandra E. Henderson, M.D.**, is a Guest Researcher in the DESPR OD. She is an associate professor of Obstetrics and Gynecology at the Albert Einstein College of Medicine, Bronx, New York.

**Peter C. Scheidt, M.D., M.P.H.**, returned to the NICHD from George Washington University to plan the Longitudinal Cohort Study of Environmental Effects on Child Health and Development. His principal research has focused on the epidemiology and prevention of injuries in children. Additional research interests include developmental effects of neonatal jaundice, environmental exposure to non-ionizing radiation in children, innovations in medical education, and behavioral pediatrics. Currently, Dr. Scheidt serves as co-principal investigator of the U.S. portion of the World Health Organization's Study of Health Behavior in School Children.

**Barbara Wingrove, M.P.H.**, is a health science administrator who serves as the project coordinator of the NICHD-D.C. Infant Mortality Initiative.

**Nancy D. Wirth** is the secretary for Dr. Klebanoff and the lead secretary in the Division. She also provides administrative support to Division staff.

### EPIDEMIOLOGY BRANCH

**Germaine M. Buck, Ph.D.**, has been Chief of the Epidemiology Branch since September 2000. Dr. Buck's primary research interests are human fecundity and fertility, especially in relation to environmental agents, such as chemicals. Her secondary research interests include promising methods and statistical approaches for reproductive and perinatal epidemiology. She has served on several committees and boards for the National Academy of Sciences, the American College of Epidemiology, and the Society for Pediatric and Perinatal Epidemiological Research.

**Ruth Brenner, M.D., M.P.H.**, tenure-track investigator, is a pediatrician/epidemiologist who joined the Epidemiology Branch in 1991. Dr. Brenner's primary research interest is in the epidemiology and prevention of childhood injuries, with a special emphasis on childhood drowning. Her secondary interests include identification of factors that influence parental attitudes and behaviors regarding child-rearing practices.

**Delois Brooks** has been with the Epidemiology Branch as secretary since October 1998. She is responsible for coordinating administrative support for the Branch professional staff to facilitate the scientific research program.

**Mary R. Conley, M.A.**, has been a computer specialist in the Pediatric Epidemiology Section of the Epidemiology Branch since 1991. During the last 20 years, she has specialized in the analysis of perinatal epidemiology research data, particularly research involving congenital malformations. Ms. Conley participates in all aspects of research, from database planning and maintenance to manuscript preparation.

**Lucinda England, M.D., M.S.P.H.**, postdoctoral fellow, is a pediatrician/epidemiologist who joined the Branch in 2000. Dr. England's primary research interests include: prenatal smoking, preterm delivery, intrauterine growth retardation, and autism.

**Richard J. Levine, M.D.**, joined the Epidemiology Branch in 1991. He is a fellow of the American Academy of Occupational and Environmental Medicine and is interested in the epidemiology of preeclampsia and infertility.

**Feng-Ying (Kimi) Lin, M.D., M.P.H.**, is a medical officer trained in pediatrics and public health. Her principal research interests are in conducting clinical trials of new vaccines for children, and in the epidemiology of perinatal infections.

**James L. Mills, M.D., M.S.**, is a pediatrician/epidemiologist who heads the Pediatric Epidemiology Section of the Branch. He is interested in the etiology of birth defects, particularly in how metabolic, genetic, and environmental factors interact to produce malformations. This is his 22<sup>nd</sup> year in DESPR, where he started his research career as a medical staff fellow.

**Malla Rao, M. Eng., M.P.H.**, is a staff scientist who joined the Epidemiology Branch in 1991. He is responsible for the design and implementation of data management systems for large vaccine trials. His primary interest is in developing novel approaches to the design and analysis of vaccine trials, with secondary research interests that include studies in pediatric and perinatal epidemiology.

**Jun (Jim) Zhang, M.D., Ph.D.**, is a tenure-track investigator in reproductive epidemiology, who joined the Epidemiology Branch in 1997. His main research interests include spontaneous abortion, fetal growth, pregnancy complications, labor and delivery, and perinatal epidemiology.

#### **PREVENTION RESEARCH BRANCH**

**Bruce G. Simons-Morton, Ed.D., M.P.H.**, has been the Branch Chief since 1998. He is a behavioral scientist with training in health education, behavioral medicine, and public health. Dr. Simons-Morton formerly served as a tenured associate professor in the Center for Health Promotion Research and Development at the School of Public Health at the University of Texas Health Science Center in Houston. His primary research interests are adolescent health

behavior, behavioral interventions in applied settings, and psychosocial determinants of health behavior.

**Aria Davis Crump, Sc.D.**, was a postdoctoral fellow from 1994, to 1999. She is currently a Guest Researcher in the Prevention Research Branch. Dr. Crump has a doctorate in behavioral science and public health from the John Hopkins School of Hygiene and Public Health. She is involved in exploratory and intervention studies pertaining to adolescent reproductive health behaviors and other problem behaviors.

**Jessica Hartos, Ph.D.**, joined the Branch in 1998, as a postdoctoral fellow and is now a research fellow. She has a Ph.D. in developmental psychology and her research interests include child/adolescent adjustment, children at-risk, parent-child relations, and prevention programs.

**Denise Haynie, Ph.D., M.P.H.**, has been a staff scientist since 2000. She started in the Branch as an Intramural Research Training Award Postdoctoral Fellow in 1993, and was promoted to a research fellow in 1997. Dr. Haynie received her doctorate in developmental psychology from Catholic University and has an M.P.H. in Maternal and Child Health from the Johns Hopkins School of Hygiene and Public Health. Dr. Haynie is involved in research pertaining to adolescent health, particularly problem behavior, parenting and adolescent peer relationships.

**Lois Maiman, Ph.D.**, is a behavioral scientist with training in social psychology and public health, who joined the NICHD in 1990, and served as Branch Chief from 1992, to 1998. Dr. Maiman was formerly a tenured associate professor in the Department of Pediatrics at the University of Rochester School of Medicine and Dentistry. Her research interests are in the efficacy of behavioral interventions in medical settings, the role of health care providers in health promotion, and psychosocial determinants of health behavior.

**Tonja Nansel, Ph.D.**, has been a postdoctoral fellow since 1998. Dr. Nansel received her doctorate in community/clinical psychology from Wichita State University. Her research interests focus on prevention and health-promotion interventions within clinical settings. She is currently involved in studies pertaining to injury prevention in young children and bullying among early adolescents.

**April Ward** is the secretary to the staff of the Prevention Research Branch.

#### **BIOMETRY AND MATHEMATICAL STATISTICS BRANCH (BMSB)**

**Kai Fun Yu, Ph.D.**, received his doctorate from Columbia University and was appointed as Chief of the BMSB in 2000. He has been a member of the Branch since 1990. His research interests include longitudinal data analysis, categorical data analysis, sequential and group sequential analysis, empirical Bayes methods, and applications of probability and statistics.

**James Troendle, Ph.D.**, is a tenure-track investigator who received his doctorate from the University of Maryland and has been a member of the BMSB since 1992. His research interests

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include multiple hypothesis testing, permutation tests, and computational statistical procedures. He also is interested in the analysis of case-controlled data.

### **COMPUTER SCIENCES SECTION (CSS)**

**Ann Trumble, Ph.D.**, is head of the CSS and has been with DESPR for more than nine years. She is responsible for organizing the computer support for the 25 scientists and visiting scientists in the Division and serves as an analyst on several projects in DESPR. She is also Project Officer for a computer support contract, which involves setting priorities and ensuring that work is done efficiently and well.

**Patricia Moyer** has worked in DESPR for more than 10 years as a computer specialist. She is a statistical programmer who supports epidemiological research using various computer languages and packages on a variety of platforms. She also provides invaluable assistance to DESPR staff in using personal computers and resolving computing problems.

**Timothy Salo**, an information systems student at the Montgomery College in Montgomery County, Maryland, works part-time in the CSS. He provides support by troubleshooting problems with computer hardware and software and maintains the backup systems, which protect data stored on the personal computers and the Sun workstation.

## APPENDIX 2: PUBLICATIONS BY DESPR STAFF MEMBERS: 1998-2001

### OFFICE OF THE DIRECTOR (OD)

Caritis SN, Sibai BM, Hauth JC, Lindheimer M, **Klebanoff MA**, Thom L, et al. (1998). Low-dose aspirin to prevent preeclampsia in women at high risk. *N Engl J Med*, 338:701-705.

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**APPENDIX 3: DESPR STAFFING**

<b>OD/Branch</b>	<b>Positions requiring FTE</b>	<b>Positions not requiring FTE</b>
Office of the Director	Division Director (1)	IRTA (1)
	Secretary (1)	Guest Researcher (1)
	D.C. Initiative Administrator (1)	
	Cohort Study Director (1)	
Epidemiology Branch	Chief (1)	IRTA (1)
	Secretary (1)	
	Senior Investigators (2)	
	Investigators (2)	
	Research Fellow (1)	
	Computer Specialist (1)	
	Expert (.50)	
	Medical Officer (.50)	
Prevention Branch	Chief (1)	IRTAs (4)
	Secretary (1)	Guest Researcher (1)
	Senior Investigator (1)	
	Staff Scientist (1)	
	Research Fellow (1)	
Biometry Branch	Chief (1)	Special Volunteer (1)
	Investigator (1)	
Computer Science Section	Chief (1)	
	Computer Specialist (1)	
	Stay-in-School (1)	
<b>TOTALS</b>	<b>24</b>	<b>9</b>

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**APPENDIX 4: CONTRACTS SUPPORTED BY DESPR,  
FISCAL YEARS 1997-2000**

<b>Fiscal Year</b>	<b>Amount</b>
1997	\$3,221,367
1998	\$6,049,556
1999	\$2,515,455
2000	\$5,660,590
<b>Total (60 Contracts)</b>	<b>\$17,446,968</b>

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